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Application of triazenes for protection of secondary amines

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Abstract—Use of the phenyldiazenyl group, which serves as a protecting group for secondary amines is described in detail. The triazene protected amine is compatible with oxidative and reductive conditions as well as with strong bases (LDA, *tert*-butyllithium) and alkylating reagents. The amine is regenerated by action of trifluoroacetic acid and a suitable reducing agent (EtOH or NaH_2PO_2). © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

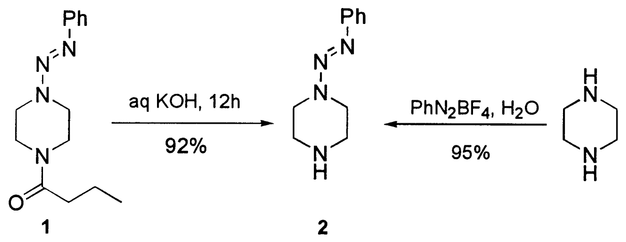
Methodology for the protection of amino groups constitutes an important field in organic synthesis, e.g. in synthesis of polypeptides, polyamines, or alkaloids. Few protecting groups, which can be used for protection of secondary amines, are resistant to harsh conditions like very strong bases.[1] Triazenes can serve as suitable protecting groups for amines due to their high stability towards bases, organolithium reagents, oxidants, reductants as well as alkylating agents.[2–6] A procedure for preparation of triazenes on an ion-exchange resin was reported by Das.[4] Triazenes can also serve as useful linkers in solid phase organic synthesis.[7,8] Use of triazenes for protection of primary aromatic amines was previously reported by Welch,[9] and for protection of secondary amines by us.[6] In this paper, we describe in detail improved procedures for protection and deprotection of amines like 4-piperidone, proline and nortropane (8-azabicyclo[3.2.1]octan-3-one). Derivatives of 4-piperidone and nortropane are of great importance to medicinal and combinatorial chemistry due to their potential biological activity.[10] To the best of our knowledge nortropane derived triazenes were not reported to date and only two reports dealt with piperidone or piperidinol based triazenes.[11,12]

2. Results and discussion

2.1. Protection of amine

Protection of secondary amines in the form of triazenes is usually a very facile and experimentally uncomplicated process. Water-soluble secondary amines (e.g. piperazine, amino alcohols like *N*-methylaminoethanol) are most conveniently protected by addition of benzenediazonium tetrafluoroborate solution to excess of amine in aqueous solution followed by excess of mild base. In the case of a precious amine, one can use an equimolar amount of the amine in the presence of pyridine. Use of triethylamine may cause a fast decomposition of the diazonium salt with evolution of nitrogen and is therefore not recommended. The formed triazene products readily separate from the aqueous phase as insoluble solids or oils. Water insoluble amines (amino esters such as proline benzyl ester) are most conveniently protected by using pyridine and methanol in dichloromethane. Methanol speeds up the process of formation of triazene by facilitating the dissolution of the diazonium salt. Although alcohols can reduce diazonium ions,[13] such reaction is usually slower under these conditions than coupling with a secondary amine. Protected amines made by this procedure are often coloured (deep red). This is caused by minor impurities (dyes), which can be removed by careful chromatography or treatment with charcoal.

We have used both aqueous and non-aqueous protection protocols to prepare derivatives of piperazine (Scheme 1). Piperazine was monoprotected with the diazenyl group to give the triazene **2** in 95% yield. Alternatively, this



Scheme 1.

Keywords: amino acid and derivatives; amino ketones; protecting groups; triazenes.

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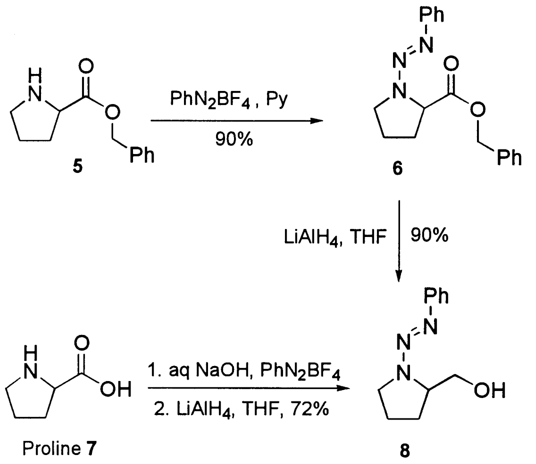
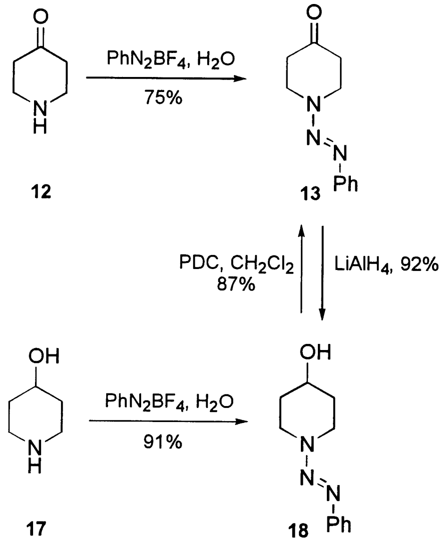
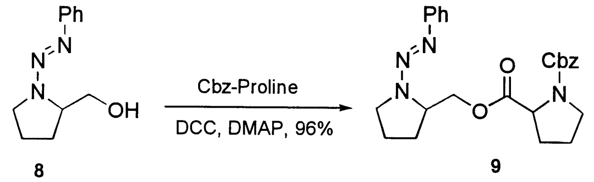


Scheme 2.

compound is accessible starting from *N*-butyrylpiperazine, through protection with the diazenyl group (85% yield) to give bisprotected piperazine **1**, followed by amide hydrolysis to give **2** (92% yield). Protection under non-aqueous conditions was also used to introduce diazenyl group on the nitrogen atom of proline benzyl ester **5** (Scheme 2) with 90% yield. The reaction of an unprotected amino acid (e.g. proline) in basic aqueous solution with a diazonium salt could also be used to protect the nitrogen atom. However, the resulting isolated protected amino acid was not stable and had to be used immediately in the next step, i.e. reduction, which gave protected prolinol **8** (72% yield over two steps). A limitation of these methods of protection is reactivity and instability of starting materials. This was evident in efforts to protect β-amino ketones (Mannich bases) such as 4-piperidone **12** and nortropinone. The *N*-phenyldiazo-4-piperidone **13** could be prepared from **12** (hydrochloride) in 75% yield (Scheme 3). However, reaction of nortropinone (HCl salt), with the diazonium salt did not give the protected product in good yield under the same conditions. This most likely stems from the tridentate nature of nortropinone as nucleophile. By analogy with tropinone one can expect that nortropinone can react with electrophiles at nitrogen, carbon or oxygen.[14] As a result of these side reactions the desired product could be isolated in 10–20% yield only. The problem of preparation of *N*-phenylazonortropinone **21** was circumvented by protection of the amino alcohol, i.e. nortropine **19** in 90% yield followed by oxidation to give protected nortropane **21** in 84% yield (Scheme 4). The same approach was also more effective in the case of preparation of 4-piperidone derivative (Scheme 3). The 4-hydroxypiperidine **17** was protected to give **18** (91% yield), which was in turn oxidized to protected piperidone **13** (87% yield).



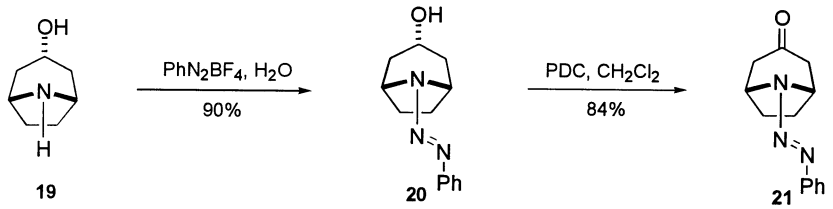
Scheme 3.



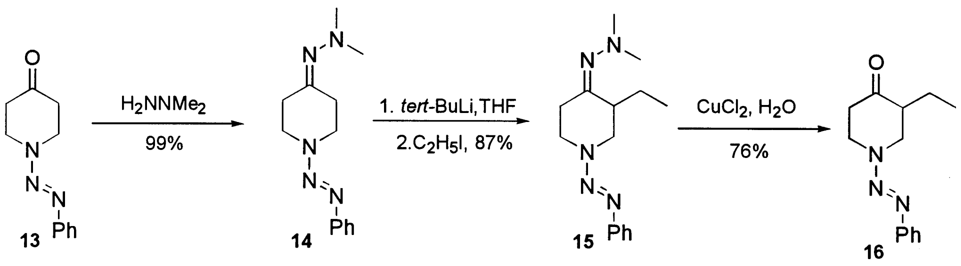
Scheme 5.

2.2. Reactions

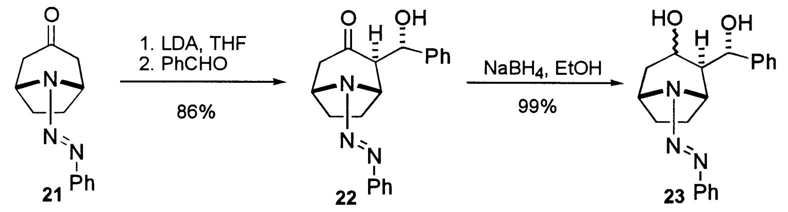
We have found that the triazene protected amino alcohols or monoprotected diamines could be acylated, alkoxycarbonylated or alkylated under typical conditions (e.g. Ac_2O, Et_3N; CbzCl, K_2CO_3; NaH, BnCl, respectively) without affecting the triazene group as long as the reaction medium remained basic or neutral. The amide hydrolysis of **1** in boiling KOH solution for 12 h to give **2** shows an extreme resistance of triazenes to bases (Scheme 1). The hydroxy group of the protected amino alcohols **18** and **20** could be oxidized to ketones with PDC under typical conditions (PDC, CH_2Cl_2, Schemes 3 and 4) and the resulting ketones could be reduced back to alcohols with sodium borohydride or lithium aluminum hydride. The latter reagent did not affect the protecting group during reduction of the protected esters or acids to alcohols in boiling THF as exemplified by preparation of proline derivative **8** (Scheme 2). The esterification of the triazene protected prolinol **8** with carbobenzyloxyproline promoted with DCC/DMAP was uneventful (Scheme 5).



Scheme 4.

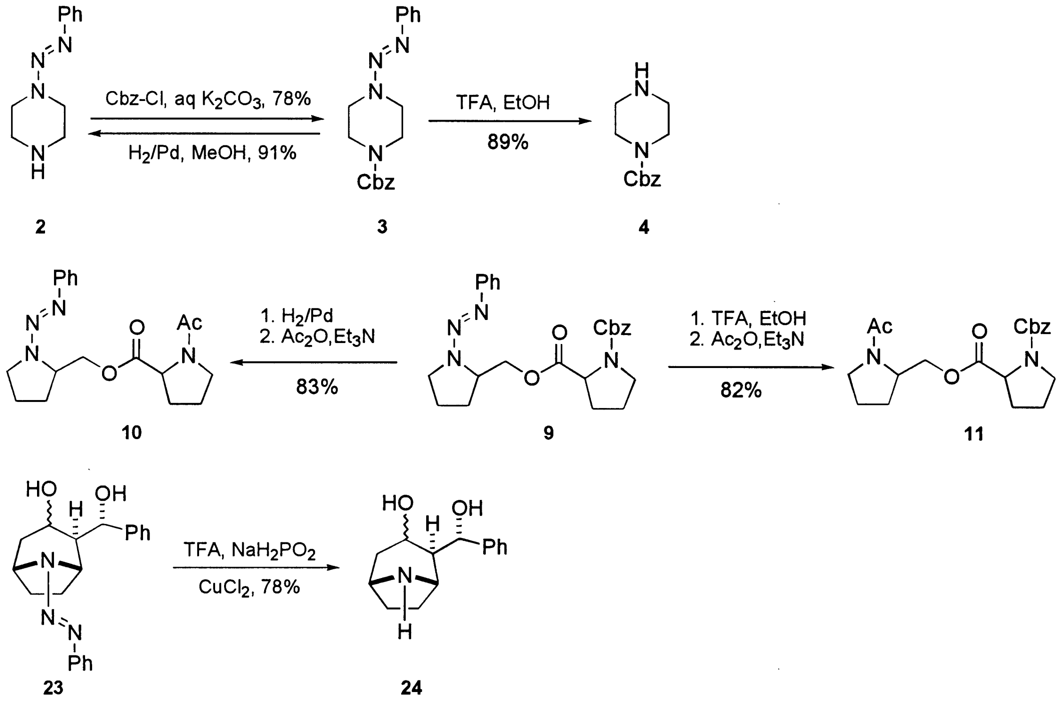


Scheme 6.



Scheme 7.

Deprotonation/lithiation of protected nortropinone **21** and protected dimethylhydrazone of 4-piperidone **14** showed that the protecting group was inert to alkyllithium reagents (e.g. *tert*-butyllithium) and lithium amide bases (LDA). The resulting lithium azaenolate and lithium enolate reacted as expected with electrophiles, e.g. ethyl iodide (Scheme 6) and benzaldehyde (Scheme 7), respectively. There was, however, detectable reduction of reactivity of lithiated/deprotonated reagents towards electrophiles. This could be explained by increased steric hindrance or stabilizing enolate/azaenolate internal complexation of lithium. The yield of the aldol product **22** was low unless 2.5–3 equiv. of LDA were used. Even then, the yield of the aldol **22** was lower than the yield of analogous *N*-methyl derivative in reaction of tropinone with benzaldehyde run under the same conditions. The aldol reaction of the protected nortropinone was also less diastereoselective (*exo*/*endo* 5:1) as indicated by NMR spectrum of the crude aldol product. The relative configuration of the aldol **22** was not determined but could be predicted to be *exo–anti* (as shown in Scheme 7) by analogy with tropane derivative.[15] Moreover, formation of the *exo* product by approaching electrophile should be favored by steric and stereoelectronic effects. The vicinal coupling constant of the PhC*H*(OH) proton was 9.5 Hz. Therefore the *anti* orientation of the aldol hydroxy group could be inferred from the large vicinal coupling



Scheme 8.

constant which is often indicative of *anti* configuration.[16] Reduction of carbonyl group in **22** with $NaBH_4$ was modestly stereoselective (2:1). The mixture of isomers in **23** was difficult to separate and was used for deprotection without separation. The described transformations show stability of the phenylazo protected amines to various reaction conditions.

2.3. Deprotection

We observed that triazenes undergo facile cleavage to amine and diazonium salt under influence of Brønsted acids. However, the process of deprotection could take many hours at room temperature. One can drive the equilibrium reaction to completion by including a reducing agent in the reaction mixture in order to reduce the diazonium ion formed. Several reagents have been used for reduction of diazonium ions among them alcohols,[13] hypophosphorus acid[17] and recently trichlorosilane.[18] We chose to use the most simple and inert reagents and conditions. The experimentally simplest and most economical method was ethanol/trifluoroacetic acid or ethanol/aq. HCl, when less mild conditions can be tolerated. Typical reaction times are 5–12 h at rt. This can be shortened to 30 min when sodium hypophosphite and copper salts are included in the reaction mixture. Thus, treatment of protected piperazine **3** or proline ester **9** with TFA in ethanol solution over night resulted in selective deprotection of triazene protected amine functionalities in good yields (89 and 83%, respectively, Scheme 8). The Cbz groups in **3** and **9** could be removed by hydrogenolysis under typical conditions without affecting the triazenes (Scheme 8). This demonstrates orthogonality of Cbz and triazene protecting groups. The deprotected proline derivatives were acetylated to give **10** and **11** in order to facilitate isolation and characterization. The protected nortropane derived amino diol **23** was subjected to $TFA/NaH_2PO_2/CuCl_2$, which resulted in fast removal of phenyldiazo group with evolution of nitrogen gas (Scheme 8, 78%). However, reaction of aldol **22** under the same conditions led to decomposition. This could be a result of a very sensitive nature of the aldol which can undergo several reactions under acidic conditions. Among them are isomerization, retroaldolization, elimination and retro Mannich reaction. The observations described show that triazene protected amines can be deprotected under mild conditions; however the limitations of this method are sensitivity of substrates and products to acids.

3. Conclusions

We have demonstrated some of the possible applications of phenyl triazene as a protecting group for secondary amines. The protecting group shows resistance to oxidants, metal hydrides, alkyllithiums, lithium amide bases and reducing agents but is not resistant to acids. Advantages of the protecting group include low cost, ease of protection (PhN_2BF_4, pyridine) and deprotection (e.g. acid/ethanol, acid/hypophosphite/Cu salt), orthogonality with carbobenzyloxy (and benzyl) group and extreme resistance to strong bases.

4. Experimental

4.1. General

All air sensitive reactions were carried out under argon. Tetrahydrofuran was distilled under argon from sodium/benzophenone. Diisopropylamine was distilled from calcium hydride. Chromatographic purifications were achieved by dry-column flash chromatography (DFC).[19] Thinlayer chromatography (TLC) was performed on precoated plates (Merck, silica gel 60, F254). The spots were detected using UV light (254 nm), and phosphomolybdic acid followed by charring. Mass spectra were recorded with an AMD-604 spectrometer and are reported as *m/z* ratio (relative intensity). Electron impact (EI) ionization was accomplished at 70 eV. Infrared (IR) spectra were recorded on a Nicolet Magna-IR 550 FTIR Series II Spectrometer as $CHCl_3$ solutions. Only diagnostic peaks are reported (cm^{-1}). Magnetic resonance spectra (^1H- and ^{13}C-NMR) were recorded on a Bruker 200 spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in ppm downfield of tetramethylsilane.

4.1.1. 4-Phenylazo-1-butyrylpiperazine (1). To a cooled (0°C) and stirred suspension of PhN_2BF_4 (0.57 g, 3.0 mmol) in CH_2Cl_2 (10 mL) and methanol (5 mL), was added butyrylpiperazine (0.44 g, 2.82 mmol) in CH_2Cl_2 (3 mL), followed by pyridine (0.55 mL, 0.4 g, 3.95 mmol). The reaction mixture was allowed to warm up to rt and stirring was continued until solids dissolved. Then the mixture was washed with aq. K_2CO_3 (20%, 20 mL). The organic layer was dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by DFC (10–50% AcOEt/hexane) and treatment with charcoal to give **1** (0.62 g, 85%) as an orange solid, mp 76–79°C; [Found: C, 64.30; H, 7.56; N, 21.13. $C_{14}H_{20}O_4N$ requires C, 64.59; H, 7.74; N, 21.52%]; R_f (30% AcOEt/hexane) 0.33; $\nu_{max}(CHCl_3)$ 1635 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) 7.48–7.27 (m, 5H), 3.68 (m, 6H), 3.47–3.42 (m, 2H), 2.22 (t, *J*=7.5 Hz, 2H), 1.66–1.55 (m, 2H), 0.92 (t, *J*=7.5 Hz, 3H); δ_C (50.3 MHz, $CDCl_3$) 171.1, 149.5, 128.5, 126.1, 120.4, 46.8 br, 44.1, 40.3, 34.6, 18.2, 13.6; *m/z* 260 (9 M^+), 105 (78), 85 (16), 77 (100), 57 (13), 56 (10), 55 (11), 51 (9%).

4.1.2. 1-Phenylazopiperazine (2). *Procedure A.* To a stirred solution of piperazine (1.3 g, 15 mmol) in water (100 mL), was added a solution of PhN_2BF_4 (0.96 g, 5 mmol) in water (30 mL). The resulting mixture was treated with aqueous solution of KOH (2 M, 5 mL). Then the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined extracts were dried ($MgSO_4$) and evaporated under vacuum. The residue was subjected to DFC (10–15% $MeOH/CH_2Cl_2$), which gave the pure **2** (0.91 g, 95%) as an orange solid.

Procedure B. A mixture of aq. KOH (2 M, 7 mL) and a solution of the 4-phenylazo-1-butyryloxypiperazine **1** (0.35 g, 1.35 mmol) in ethanol (4 mL) was heated at reflux for 12 h. After cooling to rt the reaction mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined extracts were dried ($MgSO_4$) and evaporated under vacuum to give **2** (0.24 g, 92%) as an orange solid, mp 145–147°C (from hexane/CH_2Cl_2); [Found: C, 63.09; H, 7.46; N, 29.44. $C_{10}H_{14}N_4$ requires C, 63.13; H, 7.42; N, 29.45%]; R_f (10% MeOH/CH_2Cl_2) 0.4; $\nu_{max}(CHCl_3)$ 3340 cm^{-1} (NH); δ_H (200 MHz, $CDCl_3$) 7.48–7.18 (m, 5H), 3.80–3.75 (m, 4H), 3.05–2.99 (m, 4H), 1.73 (s, 1H); δ_C (50.3 MHz, $CDCl_3$) 150.0, 128.4, 125.5, 120.2, 48.1, 44.9; *m/z* 190 (14 M^+), 105 (73), 85 (9), 78 (11), 77 (100), 56 (27), 51 (11), 42 (7%).

4.1.3. 1-Benzyloxycarbonyl-4-phenylazopiperazine (3). Solutions of benzyl chloroformate in toluene (50%, 2.2 mL, 2.25 g, 6.75 mmol) and K_2CO_3 in water (40%, 9 mL) were added portionwise to a vigorously stirred solution of 1-phenylazopiperazine **2** (1.07 g, 5.62 mmol) in CH_2Cl_2 (12 mL). After stirring for 12 h the resulting alkaline mixture was diluted and extracted with CH_2Cl_2 (3× 15 mL). The combined extracts were dried ($MgSO_4$) and evaporated under vacuum. Purification by DFC (3–30% AcOEt/hexane) gave the pure **3** (1.4 g, 78%) as an orange solid 54–57°C; [Found: C, 66.94; H, 6.24; N, 16.92. $C_{18}H_{20}O_2N_4$ requires C, 66.65; H, 6.21; N, 17.27%]; R_f (30% AcOEt/hexane) 0.55; $\nu_{max}(CHCl_3)$ 1697 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) 7.50–7.22 (m, 10H), 5.20 (s, 2H), 3.84–3.80 (m, 2H), 3.73–3.68 (m, 2H); δ_C (50.3 MHz, $CDCl_3$) 154.6, 149.6, 136.1, 128.5, 128.2, 127.8, 127.6, 126.1, 120.5, 67.0, 46.7 br, 42.7; *m/z* 324 (8 M^+), 106 (7), 105 (98), 91 (48), 78 (7), 77 (100), 65 (6), 51 (6%).

4.1.4. 1-Benzyloxycarbonylpiperazine (4). A stirred solution of 1-benzyloxycarbonyl-4-phenylazopiperazine **3** (0.22 g, 0.68 mmol) in ethanol (1.2 mL) was cooled to 0°C, and treated with TFA (1.2 mL). After 10 min, the mixture was allowed to warm up to rt and was stirred for 12 h. Then the reaction mixture was evaporated under vacuum, the residue taken up in CH_2Cl_2 (15 mL) and washed with aq. K_2CO_3. The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Purification of the residue by DFC (10–15% MeOH/hexane) and treatment with charcoal in methanol (10 mL) gave the pure **4** (0.150 g, 89%) as a yellowish oil; R_f (10% MeOH/CH_2Cl_2) 0.35; $\nu_{max}(CHCl_3)$ 1715 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) 7.26 (m, 5H), 5.07 (s, 2H), 3.93 (br s, 1H), 3.48–3.40 (m, 4H), 2.76 (m, 4H); δ_C (50.3 MHz, $CDCl_3$) 154.9, 136.3, 128.2, 127.8, 127.6, 66.9, 44.9, 43.9 br.

4.1.5. *N*-Phenylazoproline benzyl ester (6). A solution of proline benzyl ester (1 g, 5 mmol) in CH_2Cl_2 (4 mL) was added to a cooled (0°C) suspension of PhN_2BF_4 (1.2 g, 6 mmol) in CH_2Cl_2 (8 mL) and methanol (4 mL), followed by excess of pyridine (1.5 mL, 19 mmol). Stirring was continued until all solids dissolved. Then aqueous KOH (2 M, 5 mL) was added. After warming up to rt the mixture was washed with water, dried with $MgSO_4$ and concentrated under vacuum. Chromatographic purification (5–30% AcOEt/hexane) of the crude product gave **6** (1.47 g, 90%) as a yellow oil; [Found: C, 69.65; H, 6.17; N, 13.61. $C_{18}H_{19}N_3O_2$ requires C, 69.88; H, 6.19; N, 13.58%]; R_f (30% AcOEt/hexane) 0.65; $\nu_{max}(CHCl_3)$ 1740 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) 7.44–7.16 (m, 10H), 5.31–5.16 (m, 2H), 4.78 (s, 1H), 4.00 (s, 2H), 2.41–2.00 (m, 4H); δ_C (50.3 MHz, $CDCl_3$) 171.5, 150.6, 135.9, 128.6, 128.4, 128.0, 127.9, 125.8, 120.8, 66.6, 60.9 br, 49.0 br, 28.6, 22.5; *m/z* 309 (9 M^+), 106 (6), 105 (86), 91 (26), 78 (8), 77 (100), 70 (9), 51 (10%).

4.1.6. *N*-Phenylazoprolinol (8). *Procedure A*

1. To a stirred solution of proline (0.351 g, 3 mmol) in aqueous NaOH (1 M, 3 mL) was added PhN_2BF_4 (0.651 g, 3.3 mmol) in water (10 mL) at −10°C followed by NaOH (1 M, 3.3 mL). After 10 min the mixture was warmed up to rt, stirred for 30 min, acidified with citric acid solution and was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under vacuum without delay. The resulting crude red oil was immediately used in the next step.
2. Lithium aluminium hydride (0.38 g, 10 mmol) was added to a solution of the *N*-phenylazoproline (0.60 g, 2.7 mmol) in THF (8 mL), and the reaction mixture was heated under reflux for 40 min. Excess of $LiAlH_4$ was decomposed with aq. KOH solution. The solid residues were filtered off and washed with hot THF (3×5 mL). The combined filtrates were dried ($MgSO_4$) and evaporated under vacuum. The residue was subjected to DFC (10–30% AcOEt/hexane), which gave the pure **8** (0.40 g, 72%) as an orange solid.

Procedure B

To a stirred solution of *N*-phenylazoproline benzyl ester **6** (0.619 g, 2 mmol) in THF (10 mL) was added $LiAlH_4$ (0.228 g, 6 mmol) and the mixture was heated under reflux for 1 h. After cooling, the reaction mixture was worked-up as described above to give pure **8** (0.395 g, 90%) as an orange solid, mp 45–48°C; R_f (30% AcOEt/hexane) 0.32; $\nu_{max}(CHCl_3)$ 3326 cm^{-1} (OH); δ_H (200 MHz, $CDCl_3$) 7.50–7.16 (m, 5H), 4.35–4.10 (m, 1H), 3.92–3.65 (m, 4H), 2.25–1.60 (m, 5H); d_C (50.3 MHz, $CDCl_3$) 150.2, 128.6, 125.3, 120.1, 64.7 br, 62.7, 49.0 br, 26.9 br, 21.9; *m/z* 205 (52 M^+), 105 (27), 93 (8), 78 (8), 77 (100), 70 (10), 51 (15), 41 (7%); HRMS (EI); M^+, found: 205.1221. $C_{11}H_{15}ON_3$ requires 205.1215.

4.1.7. *N*-Phenylazo-2-(*N′*-benzyloxycarbonylprolyloxymethyl)pyrrolidine (9). To a cooled (0°C) solution of Cbz-proline (0.551 g, 2.2 mmol) and DCC (0.473 g, 2.3 mmol) in CH_2Cl_2 (3 mL), was added *N*-phenylazoprolinol **8** (0.41 g, 2 mmol) in CH_2Cl_2 (3 mL) followed by DMAP (0.01 g). The mixture was stirred at 0°C for 60 min, then warmed up to rt and stirred for 20 h. After wet AcOEt (1 mL) was added, the mixture was filtered. The filtrate was concentrated and the residue was purified by chromatography (DFC 10–30% AcOEt/hexane) to give **9** (0.842 g, 96%) as a yellowish oil; R_f (30% AcOEt/hexane) 0.35; $\nu_{max}(CHCl_3)$ 1745, 1698 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) 7.44–7.13 (m, 10H), 5.20–5.06 (m, 2H), 4.46–4.26 (m, 2H), 4.25–4.14 (m, 1H), 3.70–3.61 (m, 2H), 3.58–3.38 (m, 2H), 2.11–1.60 (m, 9H); δ_C (50.3 MHz, $CDCl_3$) 172.3, 154.6, 154.0, 150.8, 136.4, 128.6, 128.2, 127.7, 125.4, 120.3, 66.7, 65.3, 59.1, 58.8, 47.3 br, 46.2, 29.7, 26.9, 23.2, 21.7; *m/z* 436 (2 M^+), 331 (15), 204 (15), 160 (26), 105 (63), 91 (100), 77 (99), 70 (56%); HRMS (EI); M^+, found: 436.2119. $C_{24}H_{28}N_4O_4$ requires 436.2111.

4.1.8. *N′*-Phenylazo-2-(*N*-acetylprolyloxymethyl)pyrrolidine (10). Hydrogen gas was passed through a stirred mixture of **9** (0.193 g, 0.44 mmol), methanol (5 mL), and 10% Pd/C catalyst (0.050 g) for 60 min. Then the catalyst was filtered off and the solvent was evaporated. The resulting oil was dissolved in THF (5 mL), cooled to 0°C, and treated with acetic anhydride (0.1 mL, 1 mmol) followed by Et_3N (0.1 mL). The resulting mixture was stirred for 90 min, diluted with methanol and worked up. The extractive work-up and chromatographic purification (DFC 50% AcOEt/hexane to 10% $MeOH/CH_2Cl_2$) gave **10** (0.126 g, 83%) as a yellow oil; R_f (5% $MeOH/CH_2Cl_2$) 0.54; $\nu_{max}(CHCl_3)$ 1744, 1636 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) 7.38–7.22 (m, 5H), 4.41–4.28 (m, 4H), 3.69–3.63 (m, 2H), 3.45–3.37 (m, 2H), 2.09–1.8 (m, 11H); δ_C (50.3 MHz, $CDCl_3$) 171.8, 169.0, 150.7, 128.7, 125.2, 120.2, 65.0, 58.3, 47.3, 45.9, 31.0, 29.0, 26.8, 24.3, 21.8, 21.6; *m/z* 344 (50 M^+), 240 (14), 239 (100), 146 (18), 112 (50), 105 (46), 77 (72), 70 (52%); HRMS (EI); M^+, found: 344.1841. $C_{18}H_{24}N_4O_3$ requires 344.1848.

4.1.9. *N*-Acetyl-2-[*N′*-(benzyloxycarbonyl)prolyloxymethyl]pyrrolidine (11). Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added to a stirred solution of **9** (0.218 g, 0.5 mmol) in ethanol (0.5 mL), at 0°C. After 10 min the reaction mixture was warmed up to rt and stirred for 12 h. Then the mixture was evaporated under vacuum, diluted with CH_2Cl_2 (1 mL) and treated with Ac_2O (0.06 mL, 0.6 mmol), followed by Et_3N (1.4 mL, 10 mmol). After 2 h the mixture was diluted with methanol, and worked up. The extractive work-up and chromatographic purification (DFC 50% AcOEt/hexane to 5% $MeOH/CH_2Cl_2$) gave **11** (0.122 g, 82%) as an oil; R_f (5% $MeOH/CH_2Cl_2$) 0.54; $\nu_{max}(CHCl_3)$ 1743, 1698, 1632 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) 7.35–7.27 (m, 5H), 5.14–5.11 (m, 2H), 4.37–4.26 (m, 2H), 4.19–4.10 (m, 2H), 3.60–3.35 (m, 4H), 2.19–1.83 (m, 11H); δ_C (50.3 MHz, $CDCl_3$) 172.2, 169.4, 154.5, 153.9, 136.4, 128.2, 127.6, 66.8, 64.0, 59.0, 55.1, 47.6, 46.2, 30.6, 27.2, 23.8, 23.2, 22.5; *m/z* 374 (14 M^+), 331 (15), 239 (61), 160 (36), 126 (69), 112 (30), 91 (100), 70 (40%); HRMS (EI); M^+, found: 374.1838. $C_{20}H_{26}N_2O_5$ requires 374.1842.

4.1.10. 1-Phenylazo-4-piperidone (13). Benzenediazonium tetrafluoroborate (0.806 g, 4.2 mmol) was added to a stirred and cooled (0°C) mixture of 4-piperidone hydrochloride (0.616 g, 4 mmol), water (7 mL) and CH_2Cl_2 (7 mL). The resulting mixture was alkalized to pH=9 with $NaHCO_3$, followed by K_2CO_3, and extracted with CH_2Cl_2 (2×10 mL). The extracts were dried ($MgSO_4$) and evaporated under vacuum. The residue was subjected to DFC (20% AcOEt/hexane), which gave the pure **13** (0.612 g, 75%) as a yellowish oil; R_f (30% AcOEt/hexane) 0.50; $\nu_{max}(CHCl_3)$ 1716 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) 7.54–7.21 (m, 5H), 4.16 (t, *J*=6.5 Hz, 4H), 2.62 (t, *J*=6.5 Hz, 4H); δ_C (50.3 MHz, $CDCl_3$) 207.1, 149.9, 128.9, 126.6, 120.8, 45.6 br, 40.1; *m/z* 203 (6.5 M^+), 105 (28), 78 (7), 77 (100), 56 (5), 51 (18), 50 (4), 42 (4%); HRMS (EI); M^+, found: 203.1052. $C_{11}H_{13}ON_3$ requires 203.1059.

4.1.11. 1-Phenylazo-4-hydroxypiperidine (18). *Procedure A.* Excess of $LiAlH_4$ (0.3 g) was added to a solution of 4-phenylazo-4-piperidone **13** (0.406 g, 2 mmol) in THF (6 mL). After stirring for 20 min at rt the reaction was quenched with aq. NaOH (20%, 2 mL). An aqueous work-up gave a pure **18** (0.377 g, 92%) as a yellowish oil.

Procedure B. A solution of benzenediazonium tetrafluoroborate (0.959 g, 5 mmol) in water (10 mL) was added to a stirred mixture of 4-hydroxypiperidine (1.030 g, 10.2 mmol) and water (7 mL). The resulting mixture was made alkaline to pH=9 with K_2CO_3, and extracted with CH_2Cl_2 (4×10 mL). The extracts were dried ($MgSO_4$) and evaporated under vacuum to give the pure **18** (0.932 g, 91%) as a yellowish oil; R_f (50% AcOEt/hexane) 0.35; $\nu_{max}(CHCl_3)$ 3442 cm^{-1} (OH); δ_H (200 MHz, $CDCl_3$) 7.49–7.18 (m, 5H), 4.26–4.14 (m, 2H), 4.05–3.85 (m, 1H), 3.56–3.43 (m, 2H), 2.53 (s, OH), 2.10–1.93 (m, 2H), 1.82–1.62 (m, 2H); δ_C (50.3 MHz, $CDCl_3$) 150.3, 128.6, 125.7, 120.3, 67.7, 66.7, 44.1 br, 32.9, 25.3; *m/z* 205 (10 M^+), 105 (45), 78 (8), 77 (100), 73 (24), 51 (10), 44 (25), 42 (18%); HRMS (EI); M^+, found: 205.1213. $C_{11}H_{15}ON_3$ requires 205.1215.

4.1.12. *N,N*-Dimethylhydrazone of 1-phenylazo-4-piperidone (14). *N,N*-Dimethylhydrazine (0.5 mL, 0.397 g, 6.7 mmol) was added to a solution of 4-phenylazopiperidone **13** (0.68 g, 3.35 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 10 min at rt, then was diluted with benzene (10 mL) and the solvents were evaporated. The resulting crude **14** (0.814 g, 99%) was used in the next reaction; R_f (50% AcOEt/hexane) 0.20; $\nu_{max}(CHCl_3)$ 1638, 1594 cm^{-1} (C=N); δ_H (200 MHz, $CDCl_3$) 7.49–7.19 (m, 5H), 4.02–3.92 (m, 4H), 2.84–2.78 (m, 2H), 2.59–2.53 (m, 2H), 2.47 (s, 6H); δ_C (50.3 MHz, $CDCl_3$) 165.3, 150.1, 128.7, 126.0, 120.6, 47.2, 46.9 br, 45.6 br, 33.6, 27.6; *m/z* 245 (12 M^+), 105 (19), 97 (20), 77 (100), 56 (14), 58 (24), 51 (15), 42 (24%); HRMS (EI); M^+, found: 245.1640. $C_{13}H_{19}N_5$ requires 245.1640.

4.1.13. *N,N*-Dimethylhydrazone of 2-ethyl-1-phenylazo-4-piperidone (15). A solution of *tert*-butyllithium in pentane (0.95 mL, 1.7 M, 1.59 mmol) was added to a cooled (−78°C) solution of dimethylhydrazone of 1-phenylazo-4-piperidone **14** (0.36 g, 1.47 mmol) in THF (12 mL). After the mixture was stirred for 45 min ethyl iodide (0.14 mL, 0.264 g, 1.7 mmol) was added. The resulting mixture was stirred at −78°C for 90 min and then was allowed to warm up to rt. The reaction was quenched with aq. K_2CO_3 and extracted with ether. The extracts were dried ($MgSO_4$) and concentrated to give the crude product. Chromatographic purification (0–5% $MeOH/CH_2Cl_2$) gave **15** (0.348 g, 87%) as a yellow oil; R_f (5% $MeOH/CH_2Cl_2$) 0.55; $\nu_{max}(CHCl_3)$ 1714, 1633 cm^{-1} (C=N); δ_H (200 MHz, $CDCl_3$) 7.48–7.16 (m, 5H), 4.86–4.52 (m, 2H), 4.03–3.78 (m, 2H), 3.31–3.07 (m, 2H), 2.81–2.56 (m, 1H), 2.46 (s, 6H), 1.65–1.49 (m, 2H), 1.09–0.89 (m, 3H); δ_C (50.3 MHz, $CDCl_3$) 170.5, 150.1, 128.5, 125.7, 120.4, 68.2, 47.5, 45.1, 39.1, 23.6, 22.9, 11.4 (some peaks were split due to E/Z isomerism); *m/z* 273 (12 M^+), 105 (22), 77 (100), 58 (19), 51 (15), 44 (17), 42 (27), 41 (10%); HRMS (EI); M^+, found: 273.1952. $C_{15}H_{23}N_5$ requires 273.1953.

4.1.14. 2-Ethyl-1-phenylazo-4-piperidone (16). A solution of $CuCl_2$ (0.233 g, 1.37 mmol) in water (1.4 mL) was added to a cooled (0°C) solution of dimethylhydrazone of 2-ethyl-1-phenylazo-4-piperidone **15** (0.312 g, 1.14 mmol) in THF (3 mL). After 15 min the mixture was warmed up to rt and stirred for 60 min. Then reaction mixture was treated with 10% aq. NH_3 (3 mL) and extracted with ether (3×10 mL). The extracts were dried ($MgSO_4$) and evaporated under vacuum. The residue was subjected to DFC (0–20% AcOEt/hexane), which gave pure **16** (0.20 g, 76%) as a yellowish oil; R_f (20% AcOEt/hexane) 0.43; $\nu_{max}(CHCl_3)$ 1716 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) 7.51–7.22 (m, 5H), 4.62–4.43 (m, 2H), 3.89–3.79 (m, 1H), 3.54–3.43 (m, 1H), 2.64–2.55 (m, 2H), 2.52–2.47 (m, 1H), 1.91–1.81 (m, 1H), 1.49–1.34 (m, 1H), 1.00 (t, *J*=7.5 Hz, 3H); δ_C (50.3 MHz, $CDCl_3$) 209.0, 149.9, 128.9, 126.5, 120.8, 53.4, 50.7, 45.8 br, 39.6, 20.4, 11.4; *m/z* 231 (6 M^+), 105 (30), 78 (8), 77 (100), 51 (14), 42 (7), 41 (8), 39 (5%); HRMS (EI); M^+, found: 231.1370. $C_{13}H_{17}ON_3$ requires 231.1372.

4.1.15. *N*-Phenylazonortropine (20). A solution of benzenediazonium tetrafluoroborate (0.961 g, 5 mmol) in water (10 mL) was added to a stirred mixture of nortropine hydrochloride (0.824 g, 5 mmol) in water (7 mL). The resulting mixture was alkalized to pH=10 with aq. K_2CO_3, and extracted with CH_2Cl_2 (4×30 mL). The extracts were dried ($MgSO_4$) and evaporated under vacuum. The residue was subjected to DFC (0–20% AcOEt/hexane), which gave the pure **20** (1.040 g, 90%) as a beige solid, mp 137–140°C; R_f (50% AcOEt/hexane) 0.55; $\nu_{max}(CHCl_3)$ 3452 cm^{-1} (OH); δ_H (200 MHz, $CDCl_3$) 7.49–7.19 (m, 5H), 4.64 (br s, 2H), 4.12 (br s, 1H), 2.40–2.27 (m, 4H), 2.09–2.02 (m, 2H), 1.80 (dd, *J*=1.5, 15.0 Hz, 2H), 1.46 (br s, OH); δ_C (50.3 MHz, $CDCl_3$) 150.9, 128.8, 126.1, 120.5, 65.3, 55.0, 37.8, 26.5; *m/z* 231 (8 M^+), 105 (52), 85 (5), 83 (8), 78 (7), 77 (100), 51 (8), 41 (6%); HRMS (EI); M^+, found: 231.1369. $C_{13}H_{17}ON_3$ requires 231.1372.

4.1.16. *N*-Phenylazonortropinone (21). Pyridinium dichromate (1.554 g, 4.1 mmol) was added to a stirred solution of *N*-phenylazonortropine **20** (0.740 g, 3.2 mmol) in CH_2Cl_2 (70 mL). The mixture was stirred for 12 h and then filtered through a pad of silica. The filtrate was concentrated under vacuum to give the pure **21** (0.618 g, 84%) as a red oil; R_f (50% AcOEt/hexane) 0.67; $\nu_{max}(CHCl_3)$ 1713 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) 7.56–7.26 (m, 5H), 4.89 (br s, 2H), 2.85 (dd, *J*=4.5, 16.0 Hz, 2H), 2.46–2.38 (d, *J*=15.5, 2H), 2.26–2.17 (m, 2H), 1.87–1.80 (m, 2H); δ_C (50.3 MHz, $CDCl_3$) 207.4, 149.9, 128.7, 126.9, 120.7, 54.8, 47.3, 26.9; *m/z* 229 (9 M^+), 106 (4), 105 (44), 78 (7), 77 (100), 51 (8), 41 (5), 39 (3%); HRMS (EI); M^+, found: 229.1208. $C_{13}H_{15}ON_3$ requires 229.1215.

4.1.17. *exo–anti*-2-(1′-Hydroxybenzyl)-8-phenylazo-3-nortropanone (22). A solution of *n*-butyllithium in hexane (0.98 mL, 2.5 M, 2.44 mmol) was added dropwise to a cooled (0°C) solution of diisopropylamine (0.34 mL, 0.247 g, 2.44 mmol) in THF (12 mL). The mixture was stirred for 20 min, then cooled to −78°C. Then a solution of *N*-phenylazonortropinone (0.357 g, 1.63 mmol) in THF (2 mL) was added dropwise. After stirring for 45 min, benzaldehyde (0.20 mL, 0.208 g, 1.96 mmol) was added and the mixture was stirred for another 15 min. The reaction was quenched with aq. NH_4Cl, allowed to warm up to rt and extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated to give the crude product. Chromatographic purification (0–40% AcOEt/hexane) gave the major isomer of **22** (0.479 g, 86%) as a yellowish solid, mp 75–79°C; R_f (50% AcOEt/hexane) 0.57; $\nu_{max}(CHCl_3)$ 3452 (OH), 1712 cm^{-1} (C=O); δ_H (200 MHz, $CDCl_3$) (major isomer) 7.56–7.27 (m, 10H), 5.14 (br s, 1H), 4.95 (dd, *J*=3.0, 9.5 Hz, 1H), 4.54 (d, *J*=5.5 Hz, 1H), 3.20 (dd, *J*=3.5, 16.0 Hz, 1H), 2.72 (dt, *J*=9.5, 1.0 Hz, 1H), 2.58 (t, *J*=2.00 Hz, 1H), 2.50 (t, *J*=3.5 Hz, 1H), 2.05–1.93 (m, 2H), 1.78–1.67 (m, 2H); δ_C (50.3 MHz, $CDCl_3$) (major isomer) 209.3, 149.4, 141.2, 128.7, 128.2, 128.0, 126.9, 126.8, 120.7, 73.0, 66.1, 57.2, 54.5, 46.1, 27.2, 26.7; *m/z* 335 (6 M^+), 230 (16), 106 (11), 105 (68), 78 (8), 77 (100), 68 (8), 51 (8%); HRMS (EI); M^+, found: 335.1637. $C_{20}H_{21}O_2N_3$ requires 335.1634.

4.1.18. 2-(1′-Hydroxybenzyl)-8-phenylazo-3-nortropanol (23). To a stirred solution of **22** (0.199 g, 0.59 mmol) in ethanol was added sodium borohydride (0.068 g, 1.8 mmol). After 2 h saturated ammonium chloride (8 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3×15 mL) and the extracts were dried ($MgSO_4$) and evaporated under vacuum. The product **23** was a mixture of two isomers (0.199 g, 99%), a yellowish solid, mp 124–127°C; R_f (50% AcOEt/hexane) 0.47; $\nu_{max}(CHCl_3)$ 3452 cm^{-1} (OH); δ_H (200 MHz, $CDCl_3$) (major isomer) 7.50–7.26 (m, 10H), 5.15 (d, *J*=10.5 Hz, 1H), 4.93 (br s, 1H), 4.61–4.56 (m, 1H), 4.42 (br s, 1H), 3.95–3.70 (m, 1H), 2.22–2.06 (m, 3H), 1.86–1.62 (m, 4H), 1.30–1.19 (m, 1H); δ_C (50.3 MHz, $CDCl_3$) (major isomer) 149.8, 140.6, 128.8, 128.2, 128.0, 127.1, 126.8, 120.8, 72.9, 67.6, 59.0, 56.0, 55.0, 49.0, 36.5, 26.7; *m/z* 214 (10), 106 (9), 105 (76), 91 (9), 78 (16), 77 (100), 68 (19), 51 (9%); HRMS (ESI); $[M+1]^+$, found: 338.1857. $C_{20}H_{24}N_3O_2$ requires 338.1863.

4.1.19. 2-(1′-Hydroxybenzyl)-3-nortropanol (24). To a solution of **23** (0.339 g, 1.0 mmol) in ethanol was added solution of $NaH_2PO_2 \cdot H_2O$ (1.065 g, 10.0 mmol) in water followed by TFA (2 mL) and $CuCl_2 \cdot 2H_2O$ (0.178 g, 1.0 mmol). After 1 h the reaction mixture was alkalized with aq. KOH and aq. NH_3, and extracted with CH_2Cl_2 (3×15 mL). The combined extracts were dried ($MgSO_4$) and evaporated under vacuum. The residue was subjected to DFC (0–10% CH_2Cl_2/MeOH; 0–10% CH_2Cl_2/MeOH+NH_3), which gave the pure **24** (0.183 g, 78%) as a yellowish solid, mp 75–79°C; R_f (10% CH_2Cl_2/MeOH+NH_3) 0.44; $\nu_{max}(CHCl_3)$ 3316 cm^{-1} (NH); δ_H (200 MHz, $CDCl_3$) (major isomer) 7.43–7.26 (m, 5H), 5.13 (d, *J*=8.5 Hz, 1H), 4.05 (dt, *J*=6, 11 Hz, 1H), 3.46 (br s, 1H), 2.93 (br s, 1H), 2.08–2.02 (m, 1H), 1.86–1.75 (m, 2H), 1.56–1.46 (m, 4H); δ_C (50.3 MHz, $CDCl_3$) (major isomer) 142.9, 128.1, 127.4, 126.8, 74.4, 66.5, 56.3, 54.0, 50.4, 39.1, 29.3, 28.7; *m/z* 233 (28 M^+), 215 (100), 127 (46), 108 (72), 83 (53), 82 (48), 69 (86), 68 (62%); HRMS (EI); M^+, found: 233.1418. $C_{14}H_{19}NO_2$ requires 233.1416.

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